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REMARKS

Applicants request favorable reconsideration and allowance of this application in view of the foregoing amendments and the following remarks.

Claims 1, 4-20, 23, 24, 26-31 and 33-34 are now pending in this application, with claims 1 and 23 being independent. Claims 2, 3, 21, 22, 25 and 32 have been canceled previously, without prejudice to or disclaimer of the subject matter recited therein. Claims 5, 7, 9, 20, 23, 28 and 30 have been amended. These claim amendments place the claims in better form under U.S. practice. Claims 23, 28 and 30, in particular, have been amended to correct minor typographical errors therein. Support for the claim amendments can be found throughout the specification and in the originally-filed claims. Accordingly, no new matter has been added to this application.

At the outset, Applicants wish to thank the Examiner for acknowledging the allowability of claims 1, 6, 8, 10 to 19, 23, 24, 26, 27, 33 and 34 in the final Office Action dated May 13, 2004.

However, Applicants note that claim 4 has not been explicitly considered in the Office Action. Accordingly, Applicants kindly request that the Examiner provide a clear disposition of this claim when reviewing and responding to this Amendment.

Moreover, in the final Office Action dated May 13, 2004, claims 5, 7, 9, 20, 28, 29, 30 and 31 have been rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. In view of the amendments to the claims provided above and discussed further below, Applicants believe that this rejection is now moot and should be withdrawn.

In more detail, the Examiner has indicated that, in claims 5 and 7, it is unclear whether the terms found within parentheses further delimit the claim, and what the term "locked nucleic acid" means.

As amended, claims 5 and 7 no longer contain any terms in parentheses or any trademarked terms. Moreover, in each of these claims, the term "locked nucleic acid" has been replaced by the description of this molecule that Applicants believe is known to those having ordinary skill in the art, as evidenced by the attached document entitled "Technical Summary of Locked Nucleic Acid (LNA™) Phosphoramidites" available when visiting the Link Technologies website at http://www.linktech.co.uk/lna.htm.

Accordingly, as amended, claim 5 now further defines the gene detecting chip of claim 1, such that a plurality of different nucleotide sequences selected from the group consisting of PCR products, oligonucleotides, mRNA, cDNA, peptidic nucleic acid, and a bicyclic nucleic acid wherein a ribonucleoside is linked between the 2'-oxygen and 4'-carbon atoms with a methylene unit, is immobilized to said pin electrodes.

Moreover, as amended, claim 7 now further defines the gene detecting chip of claim 1 such that PCR products, oligonucleotides, mRNA, cDNA, peptidic nucleic acid or a bicyclic nucleic acid wherein a ribonucleoside is linked between the 2'-oxygen and the 4'-carbon atoms with a methylene unit, having the same nucleotide sequence, are immobilized to said pin electrodes.

In addition, the final Office Action suggests that claim 9 is indefinite because the meaning of the term "losses" is unclear. Applicants direct the Examiner's attention specifically to page 2, lines 6-7 of the specification, in which it is noted that "[g]ene loss refers to a partial deficiency in a base sequence, which sometimes becomes a cause of disease." Nonetheless, in an effort to advance the prosecution of this application, Applicants have replaced the term "losses" in claim 9 with the term "deletions," which Applicants believe is a more readily understandable term in English. In this regard, for example, Applicants direct the Examiner to the discussion about "deletions" as provided in James D. Watson, et al., Recombinant DNA, 2nd Ed., Scientific American Books, New York, 1992, at p. 43, a copy of which is attached. For example, that reference describes "deletions" as being the "removal of one or more bases." Moreover, that reference explains that mutations, such as deletions, "are responsible for inherited disorders and other diseases such as cancer that involve the alteration of genes" but "[a]t the same time ... are the source of phenotypic variation on which natural selection acts." Applicants believe that this reference reflects an ordinarily skilled person's understanding of the term "deletions" at the time of Applicants' invention.

Accordingly, as amended, claim 9 now further defines the gene detecting chip of claim 1 as being capable of detecting gene based sequences, one base substituted SNPs, substitution of several bases, point mutations, translocations, deletions, amplifications, or triplet repeats.

Finally, the final Office Action suggests that claim 20 is indefinite because it is unclear as to what structure of the gene detecting chip forms the claimed "gap". Applicants have amended

claim 20 to specify that a gap is formed between the body part and the frame part of the gene detecting chip. Thus, as amended, claim 20 now further characterizes the gene detecting chip of any one of claims 13, 14, 15 or 19 as having a gap formed between the body part and the frame part of the gene detecting chip, the pin electrodes being deployed on the supporting member so as to protrude into the gap, and a portion or entirety of the common electrode extending into the gap.

Applicants submit that both the independent and the dependent claims pending in this application should be deemed allowable. In particular, given the amendments made to claims 5, 7, 9, 20, dependent claims 28, 29, 30 and 31, which further depend from these claims, also should be deemed allowed. In addition, all of the dependent claims should be allowable, in their own right, for defining other patentable features of the present invention in addition to those recited in their respective independent claims.

Applicants also submit that this Amendment in Response to Final Office Action clearly places this application in condition for allowance. This Amendment was not presented earlier because Applicants believed that the prior Amendment placed the application in condition for allowance. Accordingly, entry of the instant Amendment, as an earnest attempt to advance prosecution and reduce the number of issues, is requested under 37 C.F.R. § 1.116.

In closing, Applicants have noticed that the Examiner has not yet returned an initialed copy of the PTO/SB/08a/b form submitted to the Office with the Second Supplemental Information Disclosure Statement on December 3, 2003. That Second Supplemental IDS cited a French-language patent document, namely, EP 0882981 A1, together with an English translation thereof. However, Applicants have received the initialed copies of PTO/SB/08a/b forms submitted with the other IDSs in this application, for which Applicants thank the Examiner. In particular, the documents cited with the Third Supplemental IDS have been considered by the Examiner, as evidenced by Applicants' receipt of the relevant PTO/SB/08a/b form. That form cited U.S. Patent No. 6,126,800 to Caillat, which happens to be an English-language document that relates to EP 08882981 A1. Consequently, it is not strictly necessary for the Examiner to return an initialed copy of the PTO/SB/08a/b form submitted with the Second Supplemental IDS.

Applicants request that the Examiner contact Applicants' undersigned representative should any matters be deemed outstanding, precluding allowance of this application. Applicants further request favorable reconsideration, withdrawal of the rejections set forth in the outstanding Office Action, and an early notice of allowance.

Dated: July 13, 2004

Respectfully submitted,

By Natalie M. Derzko

Natalie M. Derzko
Registration No.: 48,102
COVINGTON & BURLING
1201 Pennsylvania Avenue, N.W.
Washington, DC 20004-2401
(202) 662-6000

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link technologies
tools for molecular biology

3 Mallard Way, Strathclyde Business Park, Bellshill, Lanarkshire ML4 3BF, Scotland
tel: +44 (0) 1698 849911 fax: +44 (0) 1698 849922 enquiries@linktech.co.uk www.linktech.co.uk

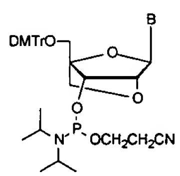
Technical Information Sheet TIS-LNA-01 v1.0

Technical Summary of Locked Nucleic Acid (LNA™) Phosphoramidites

This Technical Information Sheet refers to the following catalogue products (item numbers in brackets): LNA-Bz-A-CE Phosphoramidite (2061); LNA-methyl-Bz-C-CE Phosphoramidite (2062); LNA-dmf-G-CE Phosphoramidite (2063); and LNA-T-CE Phosphoramidite (2065).

Introduction

Locked Nucleic Acid (LNA) was first described by Wengel a co-workers in 1998[1] as a novel class of conformationally restricted oligonucleotide analogues. LNA is a bicyclic nucleic acid where a ribonucleoside is linked between the 2′-oxygen and the 4′-carbon atoms with a methylene unit. It has the general structure:



where B is one of the four protected bases (Bz-A, 5-Me-Bz-C, dmf-G, and T). Under licence from Exiqon A/S (Denmark) we offer the four standard LNA phosphoramidites.

Applications of LNA

Oligonucleotides containing LNA exhibit unprecedented thermal stabilities towards complementary DNA and RNA.[2] Additionally, LNA shows excellent mismatch discrimination. In fact the high binding affinity of LNA oligos allows for the use of short probes in e.g. SNP genotyping.[3] LNA has also produced good results in Allele specific PCR and mRNA sample preparation. In fact, LNA is recommended for use in any hybridization assay that requires high specificity and/or reproducibility e.g. dual labelled probes, *in situ* hybridization probes, molecular beacons and PCR primers. Furthermore LNA offers the possibility to adjust Tm values or primers and probes in multiplex assays.

As a result of these significant characteristics, the use of LNA-modified oligos in antisense drug development is now coming under investigation[4], and recently the therapeutic potential of LNA has been reviewed.[5]

In general, LNA oligonucleotides can be synthesised by standard phosphoramidite chemistry using DNA synthesisers. LNA can be mixed with DNA, RNA as well as other nucleic acid analogues. It can also be synthesised with modifiers and labels such as biotin, Cy dyes, etc. LNA oligonucleotides are water-soluble, can be separated by gel electrophoresis and precipitated by ethanol.

Further Information

For usage instructions in oligonucleotide synthesis please request the Technical Information Sheet *TIS-LNA-02*: **Use of Locked Nucleic Acid (LNA™) Phosphoramidites**.

The most up-to-date information on LNA phosphoramidites, including ordering information and applications, can be found by visiting the web site at www.linktech.co.uk/lna.htm.

Locked-nucleic Acid (LNA) phosphoramidites are protected by EP Pat no. 1013661, US Pat no. 6,268,490 and foreign applications and patents owned by Exiqon A/S. Products are made and sold under a license from Exiqon A/S. Products are for research purposes only. Products may not be used for diagnostic, clinical, commercial or other use, including use in humans. There is no implied license for commercial use, including contract research, with respect to the products and a license must be obtained directly from Exiqon A/S for such use.

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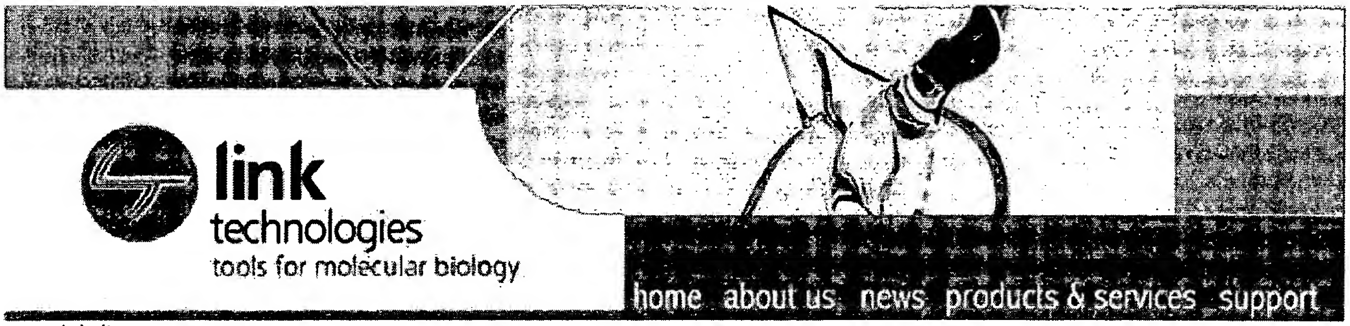
[1] (a) **Synthesis of the adenine, cytosine, guanine, 5-methylcytosine, thymine and uracil bicyclonucleoside monomers, oligomerisation, and unprecedented nucleic acid recognition**, A.A. Koshkin, S.K. Singh, P. Nielsen, V.K. Rajwanshi, R. Kumar, M. Meldgaard, C.E. Olsen, and J. Wengel, *Tetrahedron*, **54**, 3607-3630, 1998. (b) **LNA (locked nucleic acids): Synthesis and high-affinity nucleic acid recognition**, S.K. Singh, P. Nielsen, A.A. Koshkin, and J. Wengel, *Chem. Comm.*, (4), 455-456, 1998.

[2] **Investigation of restricted backbone conformations as an explanation for the exceptional thermal stabilities of duplexes involving LNA (locked nucleic acids): synthesis and evaluation of abasic LNA**, L. Kværnø and J. Wengel, *Chem. Comm.*, (7), 657-658, 1999.

[3] **SNP Genotyping using LNA (Locked Nucleic Acid)**, P. Mouritzen, A.T. Nielsen, H.M. Pfundheller, Y. Choleva, L. Kongsbak, and S. Møller, *Expert Review of Molecular Diagnostics*, **3**(1), 27-38, 2003.

[4] (a) **Design of antisense oligonucleotides stabilized by locked nucleic acids**, J. Kurreck, E. Wyszko, C. Gillen, and V.A. Erdmann, *Nucleic Acids Res.*, **30**(9), 1911-1918, 2002. (b) **Locked nucleic acids: a promising molecular family for gene-function analysis and antisense drug development**, H. Ørum and J. Wengel, *Curr. Opinion in Mol. Therap.*, **3**(3), 239-243, 2001.

[5] (a) **LNA: a versatile tool for therapeutics and genomics**, M. Petersen and J. Wengel, *Trends in Biotechnology*, **21**(2), 74-81, 2003. (b) **Novel antisense and peptide nucleic acid strategies for controlling gene expression**, D.A. Braasch, D.R. Corey, *Biochemistry*, **41**, 4503-4510, 2002.



Latest Price List

The May 2004 Price List is available to download. If you wish to be sent a paper copy then please send your full contact details to sales@linktech.co.uk.

Further Information

Technical Summary of Locked Nucleic Acid (LNA™) Phosphoramidites

Use of Locked Nucleic Acid (LNA™) Phosphoramidites

LNA: a versatile tool for therapeutics and genomics, M. Petersen and J. Wengel, *Trends in Biotechnology*, **21**(2), 74-81, 2003. [Abstract]

Tools

Design and analysis tools provided by Exiqon:

Tm prediction

OligoDesign: oligonucleotide design for expression arrays

LNA spiked SNP oligo design

Locked Nucleic Acid (LNA™) Phosphoramidites

LNA™ (Locked Nucleic Acid) is a bicyclic nucleic acid where a ribonucleoside is linked b 2'-oxygen and the 4'-carbon atoms with a methylene unit.

Oligonucleotides containing LNA nucleotides exhibit unprecedented thermal stabilities t complementary DNA and RNA. Additionally, LNA show excellent mismatch discriminatio the high binding affinity of LNA oligonucleotides allows for the use of short probes in e. genotyping.

LNA have already shown superior performance in e.g. SNP genotyping, Allele specific P sample preparation, expression profiling as well as in antisense experiments. In fact, L used in any hybridization assay that requires high specificity and/or reproducibility e.g. labelled probes, in situ hybridization probes, molecular beacons and PCR primers. Furth LNA offers the possibility to adjust Tm values of primers and probes in multiplex assays

Facts about LNA oligonucleotides:

- LNA oligonucleotides can be synthesized by standard phosphoramidite chemistr DNA-synthesizers
- LNA can be mixed with DNA, RNA as well as other nucleic acid analogs
- LNA can be synthesized with e.g. aminolinkers, biotin, Cy dyes etc
- LNA oligonucleotides are water soluble, can be separated by gel electrophoresis precipitated by ethanol

General properties of LNA oligonucleotides:

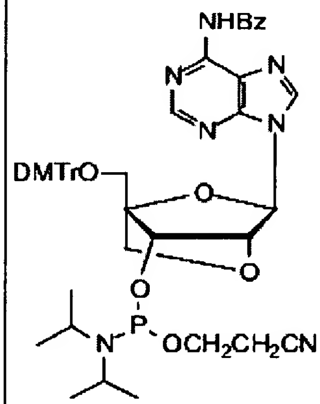
- Basepairs with DNA and RNA
- Exceptionally high thermal stability
- Improved discrimination
- Compatible with most enzymes
- Predictable melting behaviour

Catalogue Listing

Product Description	Cat. No.	Pack Size	Price (£)	P

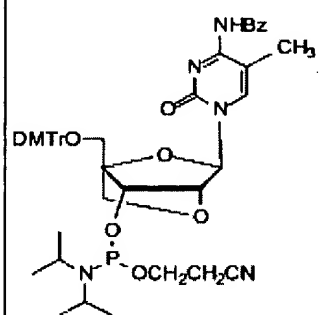
LNA spiked oligo self hybridization and secondary structure prediction

LNA-Bz-A-CE Phosphoramidite	2061-F100	100µmol	-
	2061-B250	250mg	-
	2061-B500	500mg	-
	2061-C001	1g	-



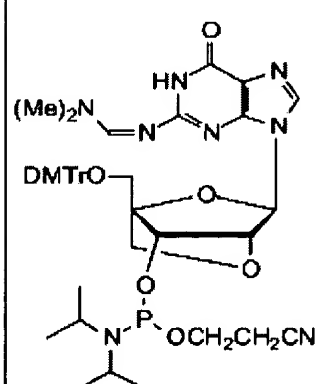
$C_{48}H_{52}N_7O_8P$ *FW* 885.96

LNA-methyl-Bz-C-CE Phosphoramidite	2062-F100	100µmol	-
	2062-B250	250mg	-
	2062-B500	500mg	-
	2062-C001	1g	-



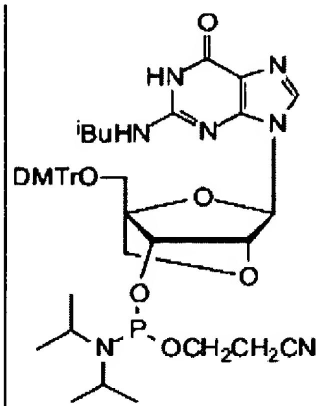
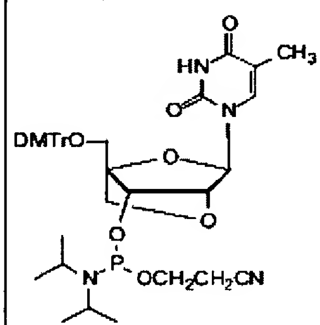
$C_{48}H_{54}N_5O_9P$ *FW* 875.96

LNA-dmf-G-CE Phosphoramidite	2063-F100	100µmol	-
	2063-B250	250mg	-
	2063-B500	500mg	-
	2063-C001	1g	-



$C_{44}H_{53}N_8O_8P$ *FW* 852.93

LNA-^{i}Bu-G-CE Phosphoramidite	2064-F100	100µmol	-
	2064-B250	250mg	-
	2064-B500	500mg	-

 $C_{45}H_{54}N_7O_9P$ *FW* 867.94	2064-C001	1g	-
LNA-T-CE Phosphoramidite	2065-F100	100µmol	-
	2065-B250	250mg	-
	2065-B500	500mg	-
$C_{41}H_{49}N_4O_9P$ *FW* 772.84	2065-C001	1g	-

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Recombinant DNA

SECOND EDITION

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ARIAD PHARMACEUTICALS, INC.

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The cover illustration, by Marvin Mattelson, symbolizes some of the elements of this book. The DNA double helix is, of course, central to the book, as it is to the cover illustration. The blocks are double-stranded DNA fragments synthesized by the polymerase chain reaction, a technique that has revolutionized the way molecular genetics experiments are done. The number of fragments doubles repeatedly, going off into the distance (see Chapter 6). The coat colors of the mice running down the helix (in the same direction but with opposite polarity!), are changing from albino to chimeric, then chimeric to agouti. These coat color changes show mice in which genetic engineering has been used to knock out a specific gene. The experiment is shown more realistically in Figure 14-9.

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be much smaller than the number of base pairs in even the smallest DNA molecule, it was concluded that most DNA molecules contain many genes.

Mutations Change the Base Sequence of DNA

Mutations arise as a change in the coding sequence of a gene. *Substitutions* occur when one base is replaced by another. In *transitions*, a purine is substituted for a purine, or a pyrimidine for a pyrimidine. In *transversions*, a purine is substituted for a pyrimidine or vice versa. *Insertions* and *deletions* are the addition and removal of one or more bases, respectively. Different mutations will have differing consequences for the function of the protein. A *nonsense mutation*, resulting from a point mutation that converts a codon to a stop codon, produces premature termination of the polypeptide chain and usually a nonfunctional protein. Because of the redundancy of the genetic code, substitutions may not lead to the incorporation of an incorrect amino acid in the protein, and even when an incorrect amino acid is used (a *missense mutation*), it may have little effect on the function of the protein unless it is in a critical portion of the protein. Deletions and insertions usually have very drastic effects on proteins because they alter the triplet groupings in which the bases are read. Mutations are important for two reasons. They are responsible for inherited disorders and other diseases such as cancer that involve alterations in genes. At the same time, mutations are the source of phenotypic variation on which natural selection acts. The process in which mutation produces variability and natural selection favors any resulting advantageous variants is the driving force of evolution.

Suppressor tRNAs Cause Misreading of the Genetic Code

Before the discovery of the double helix, *suppressor genes* had already been identified. These genes somehow have the potential to nullify the effects of specific mutations in a large variety of different genes. Now it is understood that many suppressor genes act by causing occasional misreadings of the genetic code.

The nonsense mutations can be suppressed by mutant tRNA suppressor genes. The tRNAs coded for by these genes can be charged normally with an amino acid, but because of substitutions in their bases, the anticodons of these tRNAs are now complementary to one of the stop codons. For example, there are mutant genes for tyrosine tRNA that code for the anticodon (3′)AUC(5′) instead of the correct anticodon for tyrosine, (3′)AUG(5′). The mutant anticodon recognizes the stop codon (5′)UAG(3′) instead of the appropriate tyrosine codon (5′)UAC(3′). When a mutant tyrosine tRNA comes across an internal, mutant UAG stop codon, it recognizes the stop codon and inserts a tyrosine into the polypeptide chain, allowing translation to continue. The end result is a full-length, functionally normal protein (Figure 3-7). Cells containing such a mutant tRNA suppressor gene can sur-

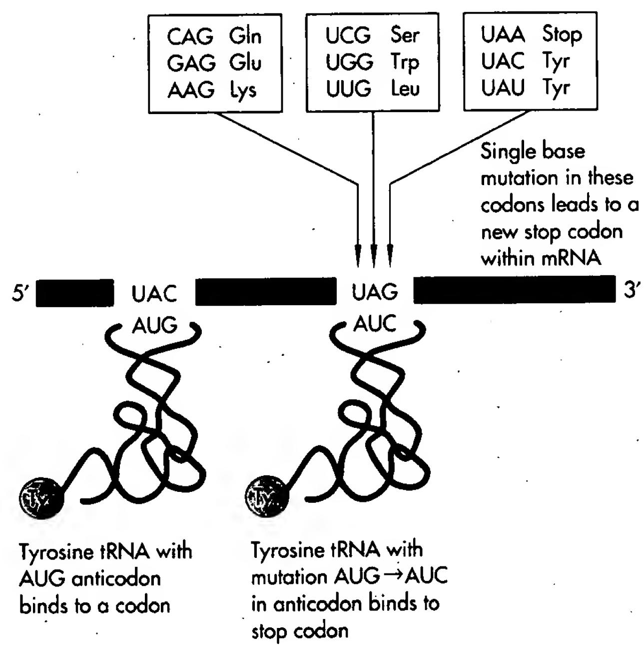

FIGURE 3-7
Suppressor tRNAs. Mutations to U, A, or G in the first, second, or third bases, respectively, of the codons listed in the boxes will lead to a UAG stop codon (nonsense mutation) within the coding region of an mRNA. One of the codons for tyrosine is (5′)UAC(3′), and the corresponding anticodon is (3′)AUG(5′). If there is a mutation in the anticodon of the tyrosine tRNA so that it becomes (3′)AUC(5′), this mutant tRNA will bind to the UAG stop codon and insert a tyrosine into the growing peptide chain. Thus synthesis of the protein will continue through the stop codon. If a tyrosine at this position restores protein function, then the nonsense mutation is suppressed.